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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/647,739	08/25/2003	Manuel Guzman Pastor	A34700 PCT USA-I	2301

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EXAMINER
ANDERSON, JAMES D

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
05/07/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/647,739	GUZMAN PASTOR ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim 16 is presented for examination

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/6/2008 has been entered.

Status of the Claims

Applicants' amendment filed 3/6/2008 has been received and entered into the application. No claims have been amended, cancelled, or added. Accordingly, claim 16 is presently under examination and is the subject of this Office Action.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Response to Arguments

Applicant's arguments filed 3/6/2008 have been fully considered but they are not persuasive. In traversing the rejection of claim 16 as being unpatentable over Sanchez in view of

Uesugi, Applicants argue that the presently claimed invention is not obvious over the cited prior art because Sanchez and Uesugi are directed to *in vitro* studies of Δ^9-tetrahydrocannabinol inducing apoptosis in C6 glioma cells. Applicants assert that there would have been no reasonable expectation that effects of a compound observed *in vitro* would also be observed *in vivo*. In support of this argument, Applicants submit a Declaration by Dr. Manuel Guzman pursuant to 37 C.F.R. 1.132.

Dr. Guzman opines that one cannot extrapolate from *in vitro* studies in the case of glioblastomas because gliomas are highly heterogenic tumors whereas a glioma cell line consists of a single homogenous population of cells. As such, Dr. Guzman asserts that while the action of a certain treatment in a glioma cell line *in vitro* is limited to its direct action over such single cell population, the effect of said treatment in an *in vivo* glioblastoma may be the result of its combined action against different tumor cell populations and non-tumor cell populations. While this may be true, the mechanism by which a compound acts is not at issue in the present case. The question is whether one of ordinary skill in the art would have been motivated to administer Δ^9-tetrahydrocannabinol or Δ^8-tetrahydrocannabinol to a mammal having a glioblastoma in view of the prior art that teaches that Δ^9-tetrahydrocannabinol induces apoptosis of C6 glioma cells *in vitro* and that such cells are an art-recognized model of glioblastomas. While it is certainly true that *in vitro* assays are not 100% predictive of *in vivo* efficacy, such is not the standard for establishing a *prima facie* case of obvious. All that is necessary is that one of ordinary skill in the art recognizes that activity *in vitro* is reasonably predictive of *in vivo* activity.

The Examiner submits herewith several non-patent literature articles teaching that activity of a compound *in vitro* reasonably correlates with activity *in vivo* with respect to

glioblastomas. All references are cited for evidentiary purposes only. Takamiya *et al.* (Neurosurgery, 1994, vol. 34, no. 5, pages 869-875) (Abstract attached) teach that the angiogenesis inhibitor, AGM-1470, inhibits the growth of human glioblastoma cells *in vitro* and *in vivo*. Piepmeier *et al.* (Cancer Research, 1996, vol. 56, pages 359-361) teach that the ribonucleoside diphosphate reductase inhibitor, MDL101731, inhibits glioblastoma cell lines *in vitro* and glioblastoma tumor growth *in vivo*. Sawa *et al.* (Acta Neuropathol., 2004, vol. 107, no. 6, pages 523-531) (Abstract attached) teach that the histone deacetylase inhibitor, FK228, induces apoptosis and suppresses cell proliferation of human glioblastoma cell *in vitro* and *in vivo*. Robe *et al.* (Clinical Cancer Research, 2004, vol. 10, pages 5595-5603) teach that sulfasalazine induces apoptosis in several glioblastoma cell lines and primary cultures *in vitro* and inhibits the growth of glioblastomas in nude mice brains *in vivo*. Thus, the prior art clearly supports the Examiner's position that one of ordinary skill in the art would have been imbued with at least a reasonable expectation of success in treating glioblastomas *in vivo* given the activity of Δ^9-tetrahydrocannabinol in inducing apoptosis of C6 glioma cells *in vitro*. This is especially true given the fact that it is well established in the prior art that Δ^9-tetrahydrocannabinol has anticancer activity in both *in vitro* and *in vivo* models of lung cancer (see Harris *et al.*, 1976, prior art of record).

Dr. Guzman also opines that the fact that a certain compound induces apoptosis *in vitro* in a tumoral cell lines does not mean that, in the case of inhibiting the tumoral growth *in vivo* the compound acts through the same mechanism. However, the Examiner respectfully submits that whether Δ^9-tetrahydrocannabinol acts by the same mechanism *in vitro* and *in vivo* is not at issue in the present rejection. The only question is whether it would have been obvious to one of

ordinary skill in the art at the time of the invention to administer Δ^9-tetrahydrocannabinol or Δ^9-tetrahydrocannabinol to a mammal having a glioblastoma. The Examiner maintains that it would have been obvious, and that one of ordinary skill in the art would reasonably expect Δ^9-tetrahydrocannabinol to be effective in inhibiting the growth of C6 glioma tumors *in vivo* as discussed *supra* and as reiterated below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claim 16 is rejected under 35 U.S.C. § 103(a) as being unpatentable over **Sanchez *et al.*** (FEBS Letters, 1998, vol. 436, pages 6-10) in view of **Uesugi *et al.*** (Acta Neuropathol., 1998, vol. 96, pages 351-356).

The instant claim recites a method of treating glioblastomas comprising administering Δ^9-tetrahydrocannabinol (Δ^9-THC) or Δ^8-tetrahydrocannabinal (Δ^8-THC).

Sanchez *et al.* disclose that Δ^9-THC induces apoptosis in C6 glioma cells (Abstract; Figures). The authors suggest that the challenge of C6.9 cells to cannabinoids may be a useful model to study the molecular mechanisms involved in apoptosis in cells of glial origin (page 9, right column).

C6 glioma cells are art-recognized as a model of glioblastomas. For example, Uesugi *et al.* discloses the use of a rat glioma cell line (C6) as a rat glioma model (Abstract; page 351). Apoptosis of glioma cells is induced by the administration of several agents, including anti-tumor drugs (*id.*). C6 glioma cells are traditionally used as a model of glioblastoma multiforme when implanted in rat brains (page 354).

In view of the teachings of the cited references, the instantly claimed method of treating glioblastomas by administering Δ^9-THC or Δ^8-THC would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made. Sanchez *et al.* demonstrate that Δ^9-THC induces apoptosis in C6 glioma cells. As such, the skilled artisan would have been motivated to use Δ^9-THC to treat glioblastomas given the fact that C6 gliomas cells were recognized in the art as a model of glioblastoma growth, invasion and metastases. Further, the skilled artisan would have been imbued with at least a reasonable expectation that a compound that induces apoptosis of C6 glioma cells *in vitro* would also be effective in treating a glioblastoma *in vivo*.

Accordingly, the claim is deemed properly rejected under 35 U.S.C. § 103 as being *prima facie* obvious over the cited references.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614

/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614